Journal of Surgical Oncology 64:331–335 (1997)

Cisplatin-Based Chemotherapy in Advanced Seminoma: Experience of the Northern Israel Oncology Center: 1981–1994

MOSHE E. STEIN, MD,[1]* ABRAHAM KUTEN, MD,[1] KEREN DRUMEA, MD,[1]
BOAZ MOSHKOWITZ, MD,[2] OFER NATIV, MD,[2] MARIANE MUNICHOR, MD,[3] AND
NISSIM HAIM MD[1]

[1]*Northern Israel Oncology Center, Rambam Medical Center, Haifa, Israel*
[2]*Department of Urology, Bnei Zion Medical Center, Haifa, Israel*
[3]*Department of Pathology, Rambam Medical Center and Faculty of Medicine, Technion, Israel Institute of Technology, Haifa, Israel*

Background: The efficacy of cisplatinum combined chemotherapy modalities was investigated in a variety of trials for patients with advanced seminoma. Results regarding remission rates and survival are encouraging.

Methods: Between December 1981 and January 1994, 13 patients with either relapsed (following radiotherapy failure) or primarily advanced seminoma were treated with cisplatin-based chemotherapy at the Northern Israel Oncology Center.

Results: Eleven (84%) patients achieved complete clearance of all sites of disease. One patient demonstrated clinically and radiographically remarkable shrinkage of an abdominal mass, and laparotomy revealed fibrotic/necrotic tissue without viable tumor cells. After a mean follow-up of 58 months (range 4–168), 12 patients (92%) are alive and well without evidence of malignancy. One patient, in whom a 2-cm abdominal mass is stable radiographically, is under observation with no sign of tumor activity. Side effects were tolerable; no patient developed chemotherapy-induced sepsis. One patient developed spontaneous pneumothorax a few days after completion of his first chemotherapy cycle, which resolved with treatment.

Conclusions: Our results confirm the efficacy and safety of cisplatin-based chemotherapy in the treatment of advanced seminoma, even in pre-irradiated patients. *J. Surg. Oncol. 64:331–335, 1997.* © 1997 Wiley-Liss, Inc.

KEY WORDS: advanced seminoma; cisplatin-based chemotherapy; high response rate

INTRODUCTION

Pure seminoma accounts for more than 40% of all cases of germ cell tumors. The clinical features that characterize seminoma include its indolent course, a predictable pattern of metastasis to regional lymph nodes, and high radiosensitivity [1]. Radiotherapy is the treatment of choice for stage I and nonbulky stage II disease [2]. For bulky stage II or metastatic disease, a cisplatin-containing regimen has been shown to be effective in inducing durable complete remission rates in 70–95% of treated patients [3]. However, study of the optimal management of patients with advanced seminoma has been hindered by its low incidence, resulting in reports with relatively few patients. The present retrospective analysis, summarizes our own experience in 13 advanced/relapsed seminoma patients treated with a cisplatin-based regimen between 1981 through 1994.

*Correspondence to: Dr. M.E. Stein, Northern Israel Oncology Center, Rambam Medical Center, P.O.B. 9602, Haifa, Israel 31096.
Accepted for publication November 20, 1996

© 1997 Wiley-Liss, Inc.

TABLE I. Relapse of Stage I Seminoma Treated Initially With Radiotherapy

Pt. No.	Age at diagnosis	Initial stage	Time to relapse (mo)	Sites of relapse	Treatment	Follow-up	Current status
1	28	I	6	Hilar/lung metastases; elevated β-HCG titer	PVB ×4; RTX	14 yr	NED; no late sequelae
2	49	I	4	Mediastinum, lung	PVB × 4; RTX; cisplatin/VP-16 ×3	13 yr	NED; mild peripheral neuropathy
3	38	I	6	Left cervical nodes	PVB ×4; RTX	10 yr	NED; no late sequelae
4	49	IIA[a]	12	Mediastinum, lung	BEP ×4	12 mo	NED

[a]Single inguinal lymph node.
β-HCG, β subunit of human chorionic gonadotropin; PVB, Einhorn combination (cisplatin, vinblastine, bleomycin); BEP, bleomycin, etoposide, cisplatin; RTX, radiotherapy; NED, no evidence of disease.

PATIENTS AND METHODS

Thirteen patients with primarily advanced or recurrent seminoma were treated with cisplatin-based chemotherapy at the Northern Israel Oncology Center. Mean age at presentation was 43 years (range 28–67). Pretreatment evaluation included physical examination, full hematologic and biochemical profile, measurement of α-fetoprotein (AFP), and β-human chorionic gonadotropin (HCG) titers, and computed tomographic (CT) scan of the thorax and abdominopelvic region. Patients were categorized as suffering from bulky stage II disease, stage IIIB disease, or visceral metastasis. Response to treatment was assessed at initial disease sites clinically, biochemically, and radiologically. Patients were treated with either cisplatin, vinblastine, bleomycin (PVB; Einhorn regimen [4]) or etoposide (VP-16), cisplatin with or without bleomycin (BEP or EP regimen).

RESULTS

Group A: Relapse Following Radiotherapy Failure

Four patients relapsed from complete remission following radiotherapy using previously described techniques [5]. The mean time to relapse was 7 months (range 4–12). All recurrences occurred outside the initial radiotherapy field (Table I). As a result of our policy in the early 1980s, consolidating post-chemo- and radiation therapy was given to initial bulky disease or to slowly regressing lymph nodes.

Patient No. 1 presented with a rising β-HCG titer and lung metastases diagnosed on routine post-radiotherapy follow-up; he was treated with four cycles of PVB and irradiated to the mediastinum/supraclavicular grooves. This patient has been without evidence of disease for 14 years.

Patient No. 2 presented initially with anaplastic seminoma, extensively infiltrating the spermatic cord and adjacent tissues. He had received wide-field radiotherapy, including the para-aortic and pelvic regions, followed by a boost to the inguinal area and left hemipelvis. Four months later, he relapsed in the mediastinum and lung. He then received the PVB regimen (four cycles), radiation therapy (to the mediastinum and both supraclavicular grooves), and a further three cycles of cisplatin and etoposide. He has been alive with no evidence of disease (NED) for 13 years.

Patient No. 3 relapsed in the left cervical nodes, for which he was given 4 cycles of PVB, and 40 Gy mediastinal irradiation with a 10-Gy boost to the cervical nodes. He has been alive and disease free for 10 years.

Patient No. 4 relapsed 12 months after having received wide-field (para-aortic, whole pelvis) irradiation with a boost to the surgical scar, both inguinal fields, and the right hemipelvis. Following four cycles of BEP, he entered virtually complete remission and has been alive and disease free for 12 months.

Toxicity

All patients developed at least one episode of neutropenic fever but with negative blood cultures, and all responded promptly to broad-spectrum antibiotics and rapid recovery of white cell count. Patient No. 2 has mild, asymptomatic lung fibrosis, confirmed on chest radiography. Patient No. 3 suffers from mild, cisplatin-induced peripheral neuropathy confined to the lower extremities. Patient No. 4 developed spontaneous pneumothorax 4 days after completion of his first chemotherapy cycle, which resolved fully following insertion of a chest tube.

Group B: Primary Advanced Seminoma

Nine patients presented with bulky or metastatic disease (Table II). Patient No. 5 underwent orchiectomy and partial resection of the involved liver prior to starting chemotherapy. He is alive with NED 3 years later. Routine post-chemotherapy consolidating radiotherapy has been abandoned during the last 10 years.

Patient No. 6 had proven metastatic seminoma in his left inguinal region. He entered a sustained complete remission after four cycles of BEP.

Patient No. 7 achieved good partial remission with

TABLE II. Primarily Advanced Seminoma Treated Initially with Cisplatin-Containing Regimen

Pt. No.	Age at diagnosis (yr)	Initial Stage/sites of disease	Treatment	Follow-up	Current status
5	67	IIIB[a]—liver metastases	Carboplatin/VP-16 ×1; cisplatin/VP-16 ×3	3 yr	NED
6	54	IIB[b]—inguinal mass, most probably of testicular origin	BEP ×4	1 yr	NED
7	50	IIC[c]	VP-16, Cisplatin ×4	12 mo	Good partial remission[e]
8	60	IIB	BEP ×3	4.5 yr	NED
9	30	IIB	BEP ×4	1.5 yr	NED
10	32	IIC[f]	BEP ×3	12 mo	Mass shrunk to 2 cm; patient under observation only
11	30	IIIA[d]	BEP ×4	12 mo	NED
12	35	IIC	BEP ×4	12 mo	NED
13	40	I[g]	BEP ×4	12 mo	NED

[a]Stage IIIB: visceral metastases.
[b]Stage IIB: abdominal node involvement 2–5-cm diameter
[c]Stage IIC: abdominal lymph node involvement >5-cm diameter or palpable mass.
[d]Stage IIIA: mediastinal and/or supraclavicular lymphadenopathy.
[e]Laparotomy demonstrated fibrotic/necrotic tissue without viable tumor cells.
[f]Initial tumor mass 6 cm.
[g]On surveillance policy; relapsed in the para-aortic lymph nodes with pathologic β-HCG and LDH levels.
BEP, bleomycin, etoposide, cisplatin; NED, no evidence of disease.

four cycles of etoposide/cisplatin regimen; bleomycin was omitted due to interstitial lung disease.

Patient No. 8 had external iliac and low para-aortic lymphadenopathy, which disappeared after the third cycle of chemotherapy, as well as an elevated β-HCG titer (67 U/L), which normalized after the first cycle.

Patient No. 9 demonstrated stage IIB disease involving the right common external iliac chain, resulting in right-sided hydronphrosis. He is alive and well 1.5 years following chemotherapy.

Patient No. 10 presented with a β-HCG level of <25 U/L. The CT scan demonstrated bulky disease, consisting of a 6-cm retroperitoneal mass above the inferior vena cava, indenting its anterior wall. Following three cycles of BEP, β-HCG titer returned to normal, and the mass shrank to 2 cm. We decided in favor of an observation policy alone.

Patient No. 11 presented with right scrotal and left supraclavicular masses. Right-sided orchiectomy demonstrated pure seminoma. β-HCG titer was 95 U/L. Following four cycles of BEP regimen, clinical, radiologic, and biochemical remission was achieved. This patient is alive and NED 12 months following completion of treatment.

Patient No. 12 demonstrated a right-sided scrotal mass, and massive retrocrural, retroperitoneal, and iliac lymphadenopathy. Orchiectomy exhibited typical seminoma. With four cycles of BEP regimen, complete remission was achieved and has been sustained for 12 months.

Patient No. 13, following right orchiectomy for stage I seminoma, chose surveillance alone. Six months postorchiectomy, he presented with a rising β-HCG (288) and lactate dehydrogtenase (LDH) (1,014) levels, plus enlarged para-aortic lymph nodes. Complete remission was obtained with four cycles of BEP, and he has been alive and NED for 12 months.

Toxicity

Two patients developed leukopenic fevers. Patients No. 8 and No. 13 continue with a mild peripheral neuropathy, while Patient No. 5 required blood and platelet transfusion due to symptomatic anemia and bleeding thrombocytopenia.

DISCUSSION

A large number of studies have indicated that advanced seminoma is very sensitive to cisplatin-containing chemotherapy. The various cisplatin-based regimens achieve a 60–90% continuous disease-free survival and a general survival rate of 78–92%. the highest durable response rate with less severe side effects was achieved with an etoposide/cisplatin regimen, even without bleomycin [6–8]. Etoposide has replaced vinblastin as it has fewer vascular side effects, such as Raynaud's phenomenon, less neuro- and myelotoxicity, and a better response rate [1].

Carboplatin, a recently introduced cisplatin analogue, has also been recommended in the treatment of advanced seminoma. However, carboplatin, either alone or in combination, has demonstrated an inferior durable complete remission rate, more hematologic toxicity, and a higher-than-expected rate of relapsed complete responders [9].

Factors such as total dose, mode of administration, and/or disease bulk did not have an impact on response or duration of response [10]. At present, carboplatin cannot be recommended as up-front therapy outside of randomized trials.

Ifosfamide has also exhibited activity in advanced seminoma. It has been incorporated into combination chemotherapy for seminoma but has not improved the results of the more standard up-front cisplatin/etoposide combination [1,11]. Its efficacy as a salvage regimen in refractory seminoma is currently being investigated [12].

Four of our patients demonstrated an elevated β-HCG titer before introduction of treatment, which returned to normal following chemotherapy. Motzer et al. [7] found that an elevated level of β-HCG was a statistically significant predictor variable, portending an inferior event-free survival. An elevated pretreatment LDH level was also associated with inferior event-free survival duration [8]. Generally, the prognostic significance of these serum tumor markers parallels that of nonseminomatous histology as predictors of treatment outcome.

Previously irradiated patients tolerate intensive chemotherapy relatively poorly, particularly following extended-field radiotherapy [13–15]. Compromised recovery of bone marrow results in a lower administered dose of cytostatic agents, delay, and even cessation of treatment. Our report does not confirm this suggestion; our previously irradiated patients tolerated the chemotherapy well with no major violations of the chemotherapy regimens. Dose modification did not have a negative impact on outcome. This is at least partly related to meticulous planning, which included less pelvic bone marrow within the radiotherapy field. No patient received prophylactic mediastinal irradiation and doses were less than 30 Gy.

Our results confirm those of Loehrer et al. [6], who stated that limited abdominal irradiation does not reduce chemotherapy tolerance significantly in subsequently relapsing patients. However, all the reported series, including our own, lack the statistical power to demonstrate this statement convincingly.

A persistent, stable but slowly resolving mass is common after chemotherapy for advanced seminoma [1]. Unlike their nonseminomatous counterparts, such masses are usually fibrotic without viable tumor cells [16]. It is accepted that masses of <3 cm do not warrant surgical excision, which is difficult and risky, but do merit close observation. A residual mass of ⩾3 cm is at high risk of a viable tumor, and surgery is indicated [17].

Side effects of initial chemotherapy are generally tolerable. They often consist of manageable leukopenia and vomiting. One of our patients (No. 4) developed spontaneous pneumothorax (SP) a few days after the first treatment. SP complicating chemotherapy has been reported mainly in chemosensitive metastatic tumors, such as osteogenic sarcoma, Wilms' tumor, and small cell lung carcinoma [18]. Only one patient with metastatic seminoma developing SP has been reported to date [19]. The proposed pathophysiological mechanisms for SP complicating chemotherapy are related to rapid rupture of chemosensitive and peripherally (subpleural) located nodules with subsequent bronchopleural fistula, previous radiation to the lung, chemotherapy-induced lysis and impaired repair process, and increased intrathoracic pressure following emetogenic chemotherapy, particularly cisplatin [18,20–22].

Our findings in general show that both primarily advanced and relapsed presentations of seminoma are very chemosensitive, and that cisplatin-based chemotherapy achieves high and sustained complete remission rates with minor side effects.

ACKNOWLEDGMENT

The authors express their appreciation to Mrs. M. Perlmutter for her assistance in preparing this manuscript.

REFERENCES

1. Horwich A, Dearnaley DP: Treatment of seminoma Semin Oncol 1992;19:171–180.
2. Epstein BE, Order SE, Zinreich ES: Staging, treatment and results in testicular seminoma: a 12 year report. Cancer 1990;65:405–411.
3. Friedman EL, Garnick MB, Stomper PC, et al: Therapeutic guidelines and results in advanced seminoma. J Clin Oncol 1985;3:1325–1332.
4. Einhorn LH, Williams SD: Chemotherapy of disseminated seminoma. Cancer Clin Trials 1980;3:307–313.
5. Stein M, Steiner M, Kuten A, et al: Testicular seminoma: results of treatment at the Northern Israel Oncology Center. Oncology 1986;43:89–92.
6. Loehrer PJ Sr, Birch R, Williams SD, et al: Chemotherapy of metastatic seminoma: the Southeastern Cancer Study Group Experience. J Clin Oncol 1987;5:1212–1220.
7. Motzer RJ, Bosl GL, Geller NL, et al: Advanced seminoma: the role of chemotherapy and adjunctive surgery. Ann Intern Med 1988;108:513–518.
8. Mencel PJ, Motzer RJ, Mazumdar M, et al: Advanced seminoma: treatment results, survival and prognostic factors in 142 patients. J Clin Oncol 1994;12:120–126.
9. Schmoll HJ, Harstrick A, Bokemeyer C, et al: Single agent carboplatinum for advanced seminoma: a phase II study. Cancer 1993;72:237–243.
10. Bajorin DF, Sarosdy MF, Pfister DG, et al: Randomized trial of etoposide and cisplatin versus etoposide and carboplatin in patients with good-risk germ cell tumors: a multi-institutional study. J Clin Oncol 1993;11:598–606.
11. Clemm C, Hartenstein R, Willich N, et al: Combination chemotherapy with vinblastine, ifosfamide and cisplatin in bulky seminoma. Acta Oncol 1989;28:231–235.
12. Motzer RJ, Cooper K, Geller NL, et al: The role of ifosfamide plus cisplatin-based chemotherapy as salvage therapy for patients with refractory germ cell tumors. Cancer 1990;66:2476–2481.
13. Logothetis CJ, Samuels ML, Ogden SL, et al: Cyclophosphamide and sequential cisplatin for advanced seminoma: long-term follow-up in 52 patients. J Urol 1987;138:789–794.
14. Fossa SD, Borge L, Aass N, et al: The treatment of advanced metastatic seminoma: experience in 55 cases. J Clin Oncol 1987;5:1071–1077.
15. Wajsman Z, Beckley SA, Pontes JE: Changing concepts in the

treatment of advanced seminomatous patients. J Urol 1983;129: 303–306.
16. Stomper PC, Jochelson MS, Friedman EL, et al: CT evaluation of advanced seminoma treated with chemothrapy. AJR 1986;146: 745–748.
17. Motzer R, Bosl G, Heelan R, et al: Residual mass: an indication for further therapy in patients with advanced seminoma following systemic chemotherapy. J Clin Oncol 1987;5:1064–1070.
18. Biran H, Dgani R, Wasserman JP, et al: Pneumothorax following induction chemotherapy in patients with lung metastatses: a case report and literature review. Ann Oncol 1992;3:297–300.
19. Chippindale AJ, Patel B, Eddleston B: Spontaneous pneumothorax with metastatic seminoma. Br J Radiol 1989;62:1100–1102.
20. Devereux DR, Thibault T, Boretos BS, et al: The quantitative and qualitative impairment of wound healing by adriamycin. Cancer 1979;43:932–938.
21. O'Connor BM, Ziegler P, Spaulding MB: Spontaneous pneumothorax in small cell lung cancer. Chest 1992;102:628–629.
22. Smevik B, Klepp O: The risk of spontaneous pneumothorax in patients with osteogenic sarcoma and testicular cancer. Cancer 1982;49:1734–1737.